B16

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C12N 15/12, 15/62, 5/10, 1/21, C07K 14/715, 16/28, A61K 38/17, 39/395

A1

(11) International Publication Number: **WO 00/08152**

(43) International Publication Date: 17 February 2000 (17.02.00)

(21) International Application Number: PCT/US99/16060

(22) International Filing Date: 16 July 1999 (16.07.99)

(30) Priority Data:
09/128,820 4 August 1998 (04.08.98) US

(71) Applicant *(for all designated States except US)*: REGENERON PHARMACEUTICALS, INC. [US/US]; 777 Old Saw Mill River Road, Tarrytown, NY 10591-6707 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: MASIAKOWSKI, Piotr, J. [PL/US]; Box 404, Halter Lane, Pleasent Valley, NY 12569 (US). MORRIS, Jodi [US/US]; 3 Bristol Court, New City, NY 10956 (US). VALENZUELA, David, M. [CL/US]; 529 Giordano Drive, Yorktown Heights, NY 10598 (US).

(74) Agents: COBERT, Robert, J.; Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591 (US) et al.

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NOVEL ORPHAN CYTOKINE RECEPTORS

(57) Abstract

The present invention provides for nucleic acid sequences that encode novel mammalian receptor polypeptides, designated HUMAN OCR10 and HUMAN OCR10-A. The invention also provides assay systems that may be used to detect and/or measure ligands that bind the HUMAN OCR10 or the HUMAN OCR10-A gene product. The present invention also provides for diagnostic and therapeutic methods based on the interaction between HUMAN OCR10 or HUMAN OCR10-A and agents that initiate signal transduction through binding to HUMAN OCR10 or HUMAN OCR10-A.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

NOVEL ORPHAN CYTOKINE RECEPTORS

This application claims priority of United States Application Serial No. 09/128,820, filed August 4, 1998, the contents of which is incorporated in its entirety by reference. Throughout this application various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application.

INTRODUCTION

The field of this invention is polypeptide molecules which regulate cell function, nucleic acid sequences encoding the polypeptides, and methods of using the nucleic acid sequences and the polypeptides. The present invention provides for novel receptor molecules, their use and assay systems useful for identifying novel ligands that interact with these receptors.

BACKGROUND OF THE INVENTION

The ability of ligands to bind cells and thereby elicit a phenotypic response such as development, differentiation, growth, proliferation, survival and regeneration in such cells is often mediated through transmembrane receptors. The extracellular portion of each receptor is generally the most distinctive portion of the molecule, as it provides the protein with its ligand-recognizing characteristic. In the case of receptor tyrosine kinases (RTKs), binding of a ligand to the

extracellular domain results in signal transduction via an intracellular tyrosine kinase catalytic domain which transmits a biological signal to intracellular target proteins. The particular array of sequence motifs of this intracellular tyrosine kinase catalytic domain determines its access to potential kinase substrates (Mohammadi, et al., 1990, Mol. Cell. Biol. 11: 5068-5078; Fantl, et al., 1992, Cell 69:413-413). For instance, growth hormone (GH) and prolactin (PRL) receptor signal transduction is mediated by a signaling system that links activation of the GH or PRL receptor at the cell surface to changes in gene transcription in the nucleus. This pathway utilizes the Jak/Stat (Janus kinase/signal transducer and activator of transcription) pathway used by many growth factors and cytokines (See Watson, et al., 1996, Rev. Reprod. 1:1-5).

The tissue distribution of a particular receptor within higher organisms provides relevant data as to the biological function of the receptor. The RTKs for some growth and differentiation factors, such as fibroblast growth factor (FGF), are widely expressed and therefore appear to play some general role in tissue growth and maintenance. Members of the Trk RTK family (Glass & Yancopoulos, 1993, Trends in Cell Biol. 3:262-268) of receptors are more generally limited to cells of the nervous system, and the neurotrophins which bind these receptors promote the differentiation of diverse groups of neurons in the brain and periphery (Lindsay, R. M, 1993, in Neurotrophic Factors, S.E. Loughlin & J.H. Fallon, eds., pp. 257-284 (San Diego, CA, Academic Press).

The cellular environment in which a receptor is expressed may influence the biological response exhibited upon binding of a ligand to the receptor. Thus, for example, when a neuronal cell expressing a Trk receptor is exposed to a neurotrophin which binds that receptor, neuronal survival and differentiation results. When the same receptor is expressed by a fibroblast, exposure to the neurotrophin results in proliferation of the fibroblast (Glass, et al., 1991, Cell 66:405-413). Thus, it appears that the extracellular domain provides the determining factor as to the ligand specificity, and once signal transduction is initiated the cellular environment will determine the phenotypic outcome of that signal transduction.

Comparison of the rat prolactin receptor sequence with that of the mammalian growth hormone receptor sequence has demonstrated some regions of identity between the two receptors, suggesting that the receptors originate from a common ancestry and may actually belong to a larger family of receptors, all of which share certain sequence homologies and perhaps related biological function. Because ligands and their receptors appear to mediate a number of important biological functions during development (e.g., bone growth, sexual maturation) as well as in the adult (e.g., homeostasis, reproduction), the identification and isolation of novel receptors may be used as a means of identifying new ligands or to study intracellular signalling pathways that may play a crucial role during development and in the maintenance of the adult phenotype. Often such novel receptors are identified and isolated by searching for additional members of known families of receptors using, for example, PCR-based screens involving known regions of homology

among receptor family members. (See, for example, Maisonpierre, et al., 1993, Oncogene 8:1631-1637). Isolation of such so called "orphan" receptors, for which no ligand is known, and subsequent determination of the tissues in which such receptors are expressed, provides insight into the regulation of the development, differentiation, growth, proliferation, survival and regeneration of cells in target tissues. Further, such receptors may be used to isolate their cognate ligands, which may then be used to regulate the development, differentiation, growth, proliferation, survival and regeneration of cells expressing the receptor.

SUMMARY OF THE INVENTION

The present invention provides for novel mammalian receptors, termed orphan cytokine receptor-10 (OCR10) and orphan cytokine receptor (OCR10)-A, which are highly expressed in human spleen, thymus, peripheral blood leukocytes, and lymph node, and expressed to a lesser extent in heart and placenta. Specifically, the present invention provides for novel human receptors termed HUMAN OCR10 and HUMAN OCR10-A. The proteins appear to be related to the cytokine family of receptors which includes, but is not limited to, the interleukin-9 receptor (IL-9R), the cytokine receptor β chain, the EPO receptor, and the leptin receptor (OB-R). The present invention further provides for an isolated nucleic acid molecule encoding HUMAN OCR10 or HUMAN OCR10-A.

The present invention also provides for a protein or polypeptide that comprises the extracellular domain of HUMAN OCR10 or HUMAN OCR10-A and the nucleic acid which encodes such extracellular domain.

The invention further provides for vectors comprising an isolated nucleic acid molecule encoding HUMAN OCR10 or HUMAN OCR10-A or its extracellular domain, which can be used to express HUMAN OCR10 or HUMAN OCR10-A in bacteria, yeast, insect or mammalian cells.

The present invention further provides for use of the HUMAN OCR10 or HUMAN OCR10-A receptor or its extracellular or intracellular domain in screening for drugs that interact with HUMAN OCR10 or HUMAN OCR10-A. Novel agents that bind to the receptor(s) described herein may mediate survival and differentiation in cells naturally expressing the receptor, but also may confer survival and proliferation when used to treat cells engineered to express the receptor. In particular embodiments, the extracellular domain (soluble receptor) of HUMAN OCR10 or HUMAN OCR10-A is utilized in screens for cognate ligands.

The invention also provides for a nucleic acid probe capable of hybridizing with a sequence included within the nucleic acid sequence encoding HUMAN OCR10 or HUMAN OCR10-A useful for the detection of HUMAN OCR10 or HUMAN OCR10-A expressing tissue in humans and animals.

The invention further provides for antibodies directed against HUMAN OCR10 or HUMAN OCR10-A.

The present invention also has diagnostic and therapeutic utilities. In particular embodiments of the invention, methods of detecting aberrancies in the function or expression of the receptor described herein may be used in the diagnosis of endocrine or immune other disorders. In other embodiments, manipulation of the receptor or agonists which bind this receptor may be used in the treatment of, for example, endocrine or immune disorders. In further embodiments, the extracellular domain of the receptor is utilized as a blocking agent which blocks the binding of ligand to target cells.

In a further embodiment of the invention, patients that suffer from an excess of HUMAN OCR10 or HUMAN OCR10-A may be treated by administering an effective amount of anti-sense RNA or anti-sense oligodeoxyribonucleotides corresponding to the HUMAN OCR10 or HUMAN OCR10-A gene coding region, thereby decreasing expression of HUMAN OCR10 or HUMAN OCR10-A.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides HUMAN OCR10 or HUMAN OCR10-A polypeptides which include isolated HUMAN OCR10 or HUMAN OCR10-A polypeptides and recombinant polypeptides comprising a HUMAN OCR10 or HUMAN OCR10-A amino acid sequence, or a functional HUMAN OCR10 or HUMAN OCR10-A polypeptide domain thereof having an assay-discernable HUMAN OCR10- or HUMAN OCR10-A-specific activity. Accordingly, the polypeptides may be deletion mutants of the disclosed HUMAN OCR10 or

HUMAN OCR10-A polypeptide and may be provided as fusion products, e.g., with non-HUMAN OCR10 or HUMAN OCR10-A polypeptides. The subject HUMAN OCR10- or HUMAN OCR10-A polypeptides have HUMAN OCR10- or HUMAN OCR10-A specific activity or function.

A number of applications for HUMAN OCR10 or HUMAN OCR10-A polypeptides are suggested from their properties. HUMAN OCR10 or HUMAN OCR10-A polypeptides may be useful in the study and treatment of conditions similar to those which are treated using cytokines and/or hormones. Furthermore, the HUMAN OCR10 or HUMAN OCR10-A cDNA may be useful as a diagnostic tool, such as through the use of oligonucleotides as primers in a PCR test to amplify those sequences having similarities to the oligonucleotide primer, and to see how much HUMAN OCR10 or HUMAN OCR10-A mRNA is present in a particular tissue or sample. The isolation of HUMAN OCR10 or HUMAN OCR10-A, of course, also provides the key to isolate its putative ligand, other HUMAN OCR10 or HUMAN OCR10-A binding polypeptides, and/or to study its properties.

HUMAN OCR10- or HUMAN OCR10-A-specific activity or function may be determined by convenient in vitro, cell based or in vivo assays. In vitro or cell based assays include but are not limited to binding assays and cell culture assays. In vivo assays include but are not limited to immune response, gene therapy and transgenic animals. Binding assays encompass any assay where the specific molecular interaction of a HUMAN OCR10 or HUMAN OCR10-A polypeptide with a binding target is evaluated. The binding target may be a natural binding target, or a non-

natural binding target such as a specific immune polypeptide such as an antibody, or a HUMAN OCR10- or HUMAN OCR10-A-specific binding agent.

The claimed HUMAN OCR10 or HUMAN OCR10-A polypeptides may be isolated or pure - an "isolated" polypeptide is one that is no longer accompanied by some of the material with which it is associated in its natural state, and that preferably constitutes at least about 0.5%, and more preferably at least about 5% by weight of the total polypeptide in a given sample; a "pure" polypeptide constitutes at least about 90%, and preferably at least about 99% by weight of the total polypeptide in a given sample. The subject polypeptides may be synthesized, produced by recombinant technology, or purified from cells. A wide variety of molecular and biochemical methods are available for biochemical synthesis, molecular expression and purification of the subject compositions, see e.g., Molecular Cloning, A Laboratory Manual (Sambrook, et al., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY), Current Protocols in Molecular Biology (Eds. Ausubel, et al., Greene Publ. Assoc., Wiley-Interscience, NY).

The subject polypeptides find a wide variety of uses including but not limited to use as immunogens, targets in screening assays, bioactive reagents for modulating cell growth, differentiation and/or function. For example, the invention provides methods for modifying the physiology of a cell comprising contacting the extracellular surface of the cell or medium surrounding the cell with an exogenous HUMAN OCR10 or HUMAN OCR10-A polypeptide under conditions whereby the

added polypeptide specifically interacts with a component of the medium and/or the extracellular surface to effect a change in the physiology of the cell. According to these methods, the extracellular surface includes plasma membrane-associated molecules. The term "exogenous HUMAN OCR10 or HUMAN OCR10-A polypeptide" refers to polypeptides not made by the cell or, if so, expressed at non-natural levels, times or physiologic locales. Media, include, but are not limited to, in vitro culture media and/or physiological fluids such as blood, synovial fluid and lymph. The polypeptides may be introduced, expressed, or repressed in specific populations of cells by any convenient way, including but not limited to, microinjection, promoter-specific expression of recombinant protein or targeted delivery of lipid vesicles.

The invention provides HUMAN OCR10- or HUMAN OCR10-A-specific binding agents, methods of identifying and making such agents, and their use in diagnosis, therapy and pharmaceutical development. HUMAN OCR10- or HUMAN OCR10-A-specific binding agents include HUMAN OCR10- or HUMAN OCR10-A-specific antibodies (See, e.g., Harlow and Lane (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY) and also includes other binding agents identified with assays such as one-, two- and three-hybrid screens, and non-natural binding agents identified in screens of chemical libraries such as described below. Agents of particular interest modulate HUMAN OCR10 or HUMAN OCR10-A polypeptide function.

The invention further provides for the production of secreted polypeptides consisting of the entire extracellular domain of HUMAN OCR10 or HUMAN OCR10-A fused to the human immunoglobulin gamma-1 constant region (IgG1 constant) or the human immunoglobulin gamma-1 Fc region (IgG1 Fc). This fusion polypeptide is called a HUMAN OCR10 or HUMAN OCR10-A "receptorbody" (RB), and would be normally expected to exist as a dimer in solution based on formation of disulfide linkages between individual IgG1 constant region or IgG1 Fc region tails. HUMAN OCR10 or HUMAN OCR10-A RB encoding nucleic acids may be part of expression vectors and may be incorporated into recombinant host cells, e.g., for expression and screening, for transgenic animals, or for functional studies such as the efficacy of candidate drugs for diseases associated with HUMAN OCR10 or HUMAN OCR10-A polypeptide-mediated signal transduction. Expression systems are selected and/or tailored to effect HUMAN OCR10 or HUMAN OCR10-A RB polypeptide structural and functional variants through alternative post-translational processing.

The invention provides HUMAN OCR10 or HUMAN OCR10-A nucleic acids, which find a wide variety of applications, including but not limited to, use as translatable transcripts, hybridization probes, PCR primers, or diagnostic nucleic acids, as well as use in detecting the presence of HUMAN OCR10 or HUMAN OCR10-A genes and gene transcripts and in detecting or amplifying nucleic acids encoding additional HUMAN OCR10 or HUMAN OCR10-A homologs and structural analogs.

The subject nucleic acids are of synthetic/non-natural sequences and/or are isolated, i.e., no longer accompanied by some of the material with which it is associated in its natural state, preferably constituting at least about 0.5%, more preferably at least about 5% by weight of total nucleic acid present in a given fraction, and usually recombinant, meaning they comprise a non-natural sequence or a natural sequence joined to a nucleotide(s) other than that to which it is joined on a natural chromosome. Nucleic acids comprising the nucleotide sequence disclosed herein and fragments thereof, contain such sequence or fragment at a terminus, immediately flanked by a sequence other than that to which it is joined on a natural chromosome, or flanked by a native flanking region fewer than 10 kb, preferably fewer than 2 kb, which is immediately flanked by a sequence other than that to which it is joined on a natural chromosome. While the nucleic acids are usually RNA or DNA, it is often advantageous to use nucleic acids comprising other bases or nucleotide analogs to provide, for example, modified stability.

The sequence of the disclosed HUMAN OCR10 or HUMAN OCR10-A nucleic acid is used to obtain the deduced HUMAN OCR10 or HUMAN OCR10-A polypeptide sequence. Further, the sequence of the disclosed HUMAN OCR10 or HUMAN OCR10-A nucleic acid is optimized for selected expression systems (Holler, et al., (1993) Gene 136:323-328; Martin, et al., (1995) Gene 154:150-166) or used to generate degenerate oligonucleotide primers and probes for use in the isolation of natural HUMAN OCR10 or HUMAN OCR10-A encoding nucleic acid sequences ("GCG" software, Genetics Computer Group, Inc., Madison, WI). HUMAN

OCR10 or HUMAN OCR10-A encoding nucleic acids may be part of expression vectors and may be incorporated into recombinant host cells, e.g., for expression and screening, for transgenic animals, or for functional studies such as the efficacy of candidate drugs for diseases associated with HUMAN OCR10 or HUMAN OCR10-A polypeptide-mediated signal transduction. Expression systems are selected and/or tailored to effect HUMAN OCR10 or HUMAN OCR10-A polypeptide structural and functional variants through alternative post-translational processing.

The invention also provides for nucleic acid hybridization probes and replication/amplification primers having a HUMAN OCR10 or HUMAN OCR10-A cDNA-specific sequence and sufficient to effect specific hybridization with SEQ. ID. NO. 1 or SEQ. ID. NO. 5. Demonstrating specific hybridization generally requires stringent conditions, for example, hybridizing in a buffer comprising 30% formamide in 5 x SSPE (0.18 M NaCl, 0.01 M $NaPO_4$, pH 7.7, 0.001 M EDTA) buffer at a temperature of 42°C and remaining bound when subject to washing at 42°C with 0.2 x SSPE; preferably hybridizing in a buffer comprising 50% formamide in 5 x SSPE buffer at a temperature of 42°C and remaining bound when subject to washing at 42°C with 0.2 x SSPE buffer at 42°C. HUMAN OCR10 or HUMAN OCR10-A cDNA homologs can also be distinguished from one another using alignment algorithms, such as BLASTX (Altschul, et al., (1990) Basic Local Alignment Search Tool, J. Mol. Biol. 215:403-410).

HUMAN OCR10 or HUMAN OCR10-A hybridization probes find use in identifying wild-type and mutant alleles in clinical and laboratory samples. Mutant alleles are used to generate allele-specific oligonucleotide (ASO) probes for high-throughput clinical diagnoses. HUMAN OCR10 or HUMAN OCR10-A nucleic acids are also used to modulate cellular expression or intracellular concentration or availability of active HUMAN OCR10 polypeptides. HUMAN OCR10 or HUMAN OCR10-A inhibitory nucleic acids are typically antisense- single stranded sequences comprising complements of the disclosed HUMAN OCR10 or HUMAN OCR10-A coding sequences. Antisense modulation of the expression of a given HUMAN OCR10 or HUMAN OCR10-A polypeptide may employ antisense nucleic acids operably linked to gene regulatory sequences. Cells are transfected with a vector comprising a HUMAN OCR10 or HUMAN OCR10-A sequence with a promoter sequence oriented such that transcription of the gene yields an antisense transcript capable of binding to endogenous HUMAN OCR10 or HUMAN OCR10-A encoding mRNA. Transcription of the antisense nucleic acid may be constitutive or inducible and the vector may provide for stable extrachromosomal maintenance or integration. Alternatively, single-stranded antisense nucleic acids that bind to genomic DNA or mRNA encoding a given HUMAN OCR10 or HUMAN OCR10-A polypeptide may be administered to the target cell, in or temporarily isolated from a host, at a concentration that results in a substantial reduction in expression of the targeted polypeptide. An enhancement in HUMAN OCR10 or HUMAN OCR10-A expression is effected by introducing into the targeted cell type HUMAN OCR10 or HUMAN OCR10-A nucleic acids which increase the functional expression of the corresponding gene

products. Such nucleic acids may be HUMAN OCR10 or HUMAN OCR10-A expression vectors, vectors which upregulate the functional expression of an endogenous allele, or replacement vectors for targeted correction of mutant alleles. Techniques for introducing the nucleic acids into viable cells are known in the art and include, but are not limited to, retroviral-based transfection or viral coat protein-liposome mediated transfection.

The invention provides efficient methods of identifying agents, compounds or lead compounds for agents active at the level of HUMAN OCR10 or HUMAN OCR10-A modulatable cellular function. Generally, these screening methods involve assaying for compounds which modulate the interaction of HUMAN OCR10 or HUMAN OCR10-A with a natural HUMAN OCR10 or HUMAN OCR10-A binding target. A wide variety of assays for binding agents are provided including, but not limited to, protein-protein binding assays, immunoassays, or cell based assays. Preferred methods are amenable to automated, cost-effective, high throughput screening of chemical libraries for lead compounds.

In vitro binding assays employ a mixture of components including a HUMAN OCR10 or HUMAN OCR10-A polypeptide, which may be part of a fusion product with another peptide or polypeptide, e.g., a tag for detection or anchoring. The assay mixtures comprise a natural HUMAN OCR10 or HUMAN OCR10-A binding target. While native binding targets may be used, it is frequently preferred to use portions thereof as long as the portion provides binding affinity and avidity to the subject HUMAN OCR10 or HUMAN OCR10-A conveniently measurable in the assay.

The assay mixture also comprises a candidate pharmacological agent. Candidate agents encompass numerous chemical classes, though typically they are organic compounds, preferably small organic compounds, and are obtained from a wide variety of sources including libraries of synthetic or natural compounds. A variety of other reagents such as salts, buffers, neutral proteins, e.g., albumin, detergents, protease inhibitors, nuclease inhibitors, or antimicrobial agents may also be included. The mixture components can be added in any order that provides for the requisite bindings and incubations may be performed at any temperature which facilitates optimal binding. The mixture is incubated under conditions whereby, but for the presence of the candidate pharmacological agent, the HUMAN OCR10 or HUMAN OCR10-A polypeptide specifically binds the binding target, portion or analog with a reference binding affinity. Incubation periods are chosen for optimal binding but are also minimized to facilitate rapid, high throughput screening.

After incubation, the agent-biased binding between the HUMAN OCR10 or HUMAN OCR10-A polypeptide and one or more binding targets is detected by any convenient way. For cell-free binding type assays, a separation step is often used to separate bound from unbound components. Separation may be effected by any number of methods that include, but are not limited to, precipitation or immobilization followed by washing by, e.g., membrane filtration or gel chromatography. For cell-free binding assays, one of the components usually comprises or is coupled to a label. The label may provide for direct detection as radioactivity, luminescence, optical or electron

density, or indirect detection such as an epitope tag or an enzyme. A variety of methods may be used to detect the label depending on the nature of the label and other assay components, including but not limited to, through optical or electron density, radiative emissions, nonradiative energy transfers, or indirectly detected with, as a nonlimiting example, antibody conjugates. A difference in the binding affinity of the HUMAN OCR10 or HUMAN OCR10-A polypeptide to the target in the absence of the agent as compared with the binding affinity in the presence of the agent indicates that the agent modulates the binding of the HUMAN OCR10 or HUMAN OCR10-A polypeptide to the corresponding binding target. A difference, as used herein, is statistically significant and preferably represents at least a 50%, more preferably at least a 90% difference.

The invention provides for a method for modifying the physiology of a cell comprising an extracellular surface in contact with a medium, said method comprising the step of contacting said medium with an exogenous HUMAN OCR10 or HUMAN OCR10-A polypeptide under conditions whereby said polypeptide specifically interacts with at least one of the components of said medium to effect a change in the physiology of said cell.

The invention further provides for a method for screening for biologically active agents, said method comprising the steps of a) incubating a HUMAN OCR10 or HUMAN OCR10-A polypeptide in the presence of a HUMAN OCR10 or HUMAN OCR10-A polypeptide-specific binding target and a candidate agent, under conditions whereby, but for

the presence of said agent, said polypeptide specifically binds said binding target at a reference affinity; b) detecting the binding affinity of said polypeptide to said binding target to determine an agent-biased affinity, wherein a difference between the agent-biased affinity and the reference affinity indicates that said agent modulates the binding of said polypeptide to said binding target.

One embodiment of the invention is an isolated HUMAN OCR10 or HUMAN OCR10-A polypeptide comprising the amino acid sequence as set forth herein or a fragment thereof having HUMAN OCR10- or HUMAN OCR10-A-specific activity.

Another embodiment of the invention is a recombinant nucleic acid encoding HUMAN OCR10 or HUMAN OCR10-A polypeptide comprising the amino acid sequence as set forth herein or a fragment thereof having HUMAN OCR10- or HUMAN OCR10-A-specific activity.

Still another embodiment is an isolated nucleic acid comprising a nucleotide sequence as set forth herein in SEQ. ID. NO. 1 or SEQ. ID. NO. 5 or a fragment thereof having at least 18 consecutive bases and which can specifically hybridize with a nucleic acid having the sequence of native HUMAN OCR10 or HUMAN OCR10-A.

The present invention also provides for antibodies to the HUMAN OCR10 or HUMAN OCR10-A polypeptides described herein which are useful for detection of the polypeptides in, for example, diagnostic applications. For preparation of monoclonal antibodies directed toward HUMAN OCR10

or HUMAN OCR10-A polypeptides, any technique which provides for the production of antibody molecules by continuous cell lines in culture may be used. For example, the hybridoma technique originally developed by Kohler and Milstein (1975, Nature 256:495-497), as well as the trioma technique, the human B-cell hybridoma technique (Kozbor et al., 1983, Immunology Today 4:72), and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole et al., 1985, in "Monoclonal Antibodies and Cancer Therapy", Alan R. Liss, Inc. pp. 77-96) and the like are within the scope of the present invention.

The monoclonal antibodies for diagnostic or therapeutic use may be human monoclonal antibodies or chimeric human-mouse (or other species) monoclonal antibodies. Human monoclonal antibodies may be made by any of numerous techniques known in the art (e.g., Teng et al., 1983, Proc. Natl. Acad. Sci. U.S.A. 80:7308-7312; Kozbor et al., 1983, Immunology Today 4:72-79; Olsson et al., 1982, Meth. Enzymol. 92:3-16). Chimeric antibody molecules may be prepared containing a mouse antigen-binding domain with human constant regions (Morrison et al., 1984, Proc. Natl. Acad. Sci. U.S.A. 81:6851, Takeda et al., 1985, Nature 314:452).

Various procedures known in the art may be used for the production of polyclonal antibodies to the HUMAN OCR10 or HUMAN OCR10-A polypeptides described herein. For the production of antibody, various host animals can be immunized by injection with the HUMAN OCR10 or HUMAN OCR10-A polypeptides, or fragments or derivatives thereof, including but not limited to rabbits, mice and rats. Various adjuvants

may be used to increase the immunological response, depending on the host species, including but not limited to Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, polypeptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (Bacille Calmette-Guerin) and Corynebacterium parvum.

A molecular clone of an antibody to a selected HUMAN OCR10 or HUMAN OCR10-A polypeptide epitope can be prepared by known techniques. Recombinant DNA methodology (see e.g., Maniatis et al., 1982, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY) may be used to construct nucleic acid sequences which encode a monoclonal antibody molecule, or antigen binding region thereof.

The present invention provides for antibody molecules as well as fragments of such antibody molecules. Antibody fragments which contain the idiotype of the molecule can be generated by known techniques. For example, such fragments include, but are not limited to, the $F(ab')_2$ fragment which can be produced by pepsin digestion of the antibody molecule; the Fab' fragments which can be generated by reducing the disulfide bridges of the $F(ab')_2$ fragment, and the Fab fragments which can be generated by treating the antibody molecule with papain and a reducing agent. Antibody molecules may be purified by known techniques including, but not limited to, immunoabsorption or immunoaffinity chromatography, chromatographic methods such as

HPLC (high performance liquid chromatography), or a combination thereof.

The following example is offered by way of illustration and not by way of limitation.

EXAMPLE 1:

OCR10 was initially detected in tblastn searches of the non-redundant nucleotide database (NT) at The National Center for Biotechnology Information (NCBI), using sequences derived from members of the cytokine receptor family as queries. The matching region corresponded to a characteristic cytokine receptor family amino acid pattern WSXWS (Bazan, J.F., 1990, PNAS 87:6934-6938), located within a BAC clone (Genebank Identification No. 2342739) derived from human chromosome 16. The nucleotide and deduced amino acid sequences of these regions correspond to nucleotides (NTs) 508-685 of SEQ. NO. 1 and amino acids 170-230 of SEQ. NO. 2 as set forth below:

```
                    10         20         30         40         50         60
                     .          .          .          .          .          .
SEQ. ID. NO. 1: ATG CCG CGT GGC TGG GCC GCC CCC TTG CTC CTG CTG CTG CTC CAG GGA GGC TGG GGC TGC
SEQ. ID. NO. 2: M  P  R  G  W  A  A  P  L  L  L  L  L  L  Q  G  G  W  G  C>

                    70         80         90         100        110        120
                     .          .          .          .          .          .
CCC GAC CTC GTC TGC TAC ACC GAT TAC CTC CAG ACG GTC ATC TGC ATC CTG GAA ATG TGG
P  D  L  V  C  Y  T  D  Y  L  Q  T  V  I  C  I  L  E  M  W>

                    130        140        150        160        170        180
                     .          .          .          .          .          .
AAC CTC CAC CCC AGC ACG CTC ACC CTT ACC TGG CAA GAC CAG TAT GAA GAG CTG AAG GAC
N  L  H  P  S  T  L  T  L  T  W  Q  D  Q  Y  E  E  L  K  D>

                    190        200        210        220        230        240
                     .          .          .          .          .          .
GAG GCC ACC TCC TGC AGC CTC CAC AGG TCG GCC CAC AAT GCC ACG CAT GCC ACC TAC ACC
E  A  T  S  C  S  L  H  R  S  A  H  N  A  T  H  A  T  Y  T>

                    250        260        270        280        290        300
                     .          .          .          .          .          .
TGC CAC ATG GAT GTA TTC CAC TTC ATG GCC GAC GAC ATT TTC AGT GTC AAC ATC ACA GAC
C  H  M  D  V  F  H  F  M  A  D  D  I  F  S  V  N  I  T  D>

                    310        320        330        340        350        360
                     .          .          .          .          .          .
CAG TCT GGC AAC TAC TCC CAG GAG TGT GGC AGC TTT CTC CTG GCT GAG AGC ATC AAG CCG
Q  S  G  N  Y  S  Q  E  C  G  S  F  L  L  A  E  S  I  K  P>

                    370        380        390        400        410        420
                     .          .          .          .          .          .
GCT CCC CCT TTC AAC GTG ACT GTG ACC TTC TCA GGA CAG TAT AAT ATC TCC TGG CGC TCA
A  P  P  F  N  V  T  V  T  F  S  G  Q  Y  N  I  S  W  R  S>

                    430        440        450        460        470        480
                     .          .          .          .          .          .
GAT TAC GAA GAC CCT GCC TTC TAC ATG CTG AAG GGC AAG CTT CAG TAT GAG CTG CAG TAC
D  Y  E  D  P  A  F  Y  M  L  K  G  K  L  Q  Y  E  L  Q  Y>

                    490        500        510        520        530        540
                     .          .          .          .          .          .
AGG AAC CGG GGA GAC CCC TGG GCT GTG AGT CCG AGG AGA AAG CTG ATC TCA GTG GAC TCA
R  N  R  G  D  P  W  A  V  S  P  R  R  K  L  I  S  V  D  S>

                    550        560        570        580        590        600
                     .          .          .          .          .          .
AGA AGT GTC TCC CTC CTC CCC CTG GAG TTC CGC AAA GAC TCG AGC TAT GAG CTG CAG GTG
R  S  V  S  L  L  P  L  E  F  R  K  D  S  S  Y  E  L  Q  V>

                    610        620        630        640        650        660
                     .          .          .          .          .          .
CGG GCA GGG CCC ATG CCT GGC TCC TCC TAC CAG GGG ACC TGG AGT GAA TGG AGT GAC CCG
R  A  G  P  M  P  G  S  S  Y  Q  G  T  W  S  E  W  S  D  P>

                    670        680        690        700        710        720
                     .          .          .          .          .          .
GTC ATC TTT CAG ACC CAG TCA GAG GAG TTA AAG GAA GGC TGG AAC CCT CAC CTG CTG CTT
V  I  F  Q  T  Q  S  E  E  L  K  E  G  W  N  P  H  L  L  L>

                    730        740        750        760        770        780
                     .          .          .          .          .          .
CTC CTC CTG CTT GTC ATA GTC TTC ATT CCT GCC TTC TGG AGC CTG AAG ACC CAT CCA TTG
L  L  L  L  V  I  V  F  I  P  A  F  W  S  L  K  T  H  P  L>

                    790        800        810        820        830        840
                     .          .          .          .          .          .
TGG AGG CTA TGG AAG AAG ATA TGG GCC GTC CCC AGC CCT GAG CGG TTC TTC ATG CCC CTG
W  R  L  W  K  K  I  W  A  V  P  S  P  E  R  F  F  M  P  L>

                    850        860        870
                     .          .          .
TAC AAG GGC TGC AGC GGA GAC TTC AAG TGA
Y  K  G  C  S  G  D  F  K  *>
```

The HMMER program (http://hmmer.wustl.edu) was used to find another region matching a cytokine receptor family amino acid pattern on the same BAC sequence. This region corresponds to a proline hinge motif PP, which is normally adjacent to the WSXWS region. The nucleotide and deduced amino acid sequences of the proline hinge motif region correspond to NTs 352-507 of SEQ. NO. 1 and amino acids 118-169 of SEQ. NO. 2, respectively. These data suggested that two exons of a novel cytokine receptor have been located on the BAC clone.

Example 2: Cloning of human OCR10 gene using PCR.

A 111-mer oligonucleotide was synthesized (Genelink, Thornwood, NY) that corresponded to NTs 568-678 of SEQ. NO. 1 for use as a PCR template. Two smaller oligonucleotides, HUMAN OCR10-1 (NTs 568-585 of SEQ. NO. 1) and HUMAN OCR10-2rc (NTs 660-678 of SEQ. NO. 1), corresponding to the outer regions of the OCR10 111-mer oligonucleotide, were also synthesized (Genelink, Thornwood, NY) and used as amplification primers using the 111-mer oligonucleotide as a template in a standard PCR reaction. The resulting PCR product was used to probe a Northern blot (CLONTECH Human Multiple Tissue Blot, Catalog #7760-1) at an overnight hybridization temperature of 65°C, a wash temperature of 65°C, and an Bio-Imaging Analyzer BAS 2000 (Fugi) exposure time of 22 hours. Faint 9.5 kb RNA transcripts were observed in two human tissues, heart and placenta.

The WSXWS and proline hinge motif region sequences were pieced together theoretically (resulting sequence corresponding to NTs 352-685 of SEQ. NO. 1) and several oligonucleotides were synthesized (Genelink, Thornwood, NY) that corresponded to specific sequences within each of these regions. These oligonucleotides were used in the following PCR reactions using standard PCR reaction conditions.

PCR reaction #1 was carried out with oligonucleotides HUMAN OCR10.5 (NTs 372-395 of SEQ. NO. 1) and HUMAN OCR10.2rc (NTs 660-678 of SEQ. NO. 1) using CLONTECH's Marathon-Ready™ cDNA derived from eight different tissues (Human Pancreas, catalog #7410-1; Human Heart, catalog # 7404-1; Human Fetal Liver, catalog # 7403-1; Human Fetal Skeletal Muscle, catalog # 7435-1; Human Fetal Spleen, catalog # 7422-1; Human Spleen, catalog # 7412-1; Human Fetal Brain, catalog # 7402-1; and Human Lung, catalog # 7408-1) as PCR templates. None of the reactions produced visible PCR products when run on a 1% agarose gel.

PCR reaction #2, a nested PCR reaction, was carried out with oligonucleotides HUMAN OCR10.6 (NTs 414-437 of SEQ. NO. 1) and HUMAN OCR10.4rc (NTs 635-658 of SEQ. NO. 1) using as the PCR templates the products of the eight PCR reactions from PCR reaction #1 *supra*. The strongest 240bp PCR fragment was obtained in human fetal spleen, human spleen, and human lung. The other tissues tested, human pancreas, heart, fetal liver, fetal skeletal muscle, and fetal brain, produced only faint 240bp PCR products.

The 240bp PCR fragment was sequenced by standard techniques using an ABI 373A DNA sequencer and Taq Dideoxy Terminator Cycle Sequencing Kit (Applied Biosystems, Inc., Foster City, CA) and found to contain DNA sequence homologous to both the WSXWS and the proline hinge motif regions. The nucleotide and deduced amino acid sequences of the 240bp PCR fragment corresponds to NTs 418-651 of SEQ. NO. 1 and amino acids 140-217 of SEQ. NO. 2, respectively.

Example 3: 5'RACE to obtain complete 5' region of HUMAN OCR10.

A 5' RACE (CLONTECH Marathon-Ready™ cDNA user manual #PT1156-1) was performed on human spleen and human lung cDNA (CLONTECH's Marathon-Ready™ cDNA, catalog #7412-1 and #7408-1, respectively) in an attempt to clone additional 5' sequence.

The first PCR reaction was performed with the 5' oligonucleotide HUMAN OCR10.2rc (NTs 660-678 of SEQ. NO. 1) and the RACE kit oligonucleotide AP1. This amplification produced no visible PCR product.

The second PCR reaction was performed with the 5' oligonucleotide HUMAN OCR10.4rc (NTs 635-658 of SEQ. NO. 1) and the RACE kit oligonucleotide AP2. PCR product smears were obtained from this reaction. Five microliters of each reaction was run on a 1% agarose gel, the gel was denatured and neutralized by standard techniques (See Current Protocols in Molecular Biology, Eds. Ausubel, et al., Greene Publ. Assoc., Wiley-Interscience, NY), dried on a Savant Slab Gel Dryer

(Savant, Holbrook, NY) and hybridized overnight at 45°C using a nested oligonucleotide probe (HUMAN OCR10.7 nt 441-465). Both of the 5'-specific RACE reaction smears ranged in size from about 200bp to 2500bp. A preparative 1% agarose gel was run and six individual slices were cut from varying regions of the smears and purified using QIAEX II Gel Extraction Kit, (catalog #20021, QIAGEN, Valencia, CA). The purified slices were subcloned into Zeroblunt (catalog #K2700-20, Invitrogen, Carlsbad, CA). The new 5' sequence (NTs 1-352 of SEQ. NO. 1) was confirmed using an ABI 373A DNA sequencer and Taq Dideoxy Terminator Cycle Sequencing Kit (Applied Biosystems, Inc., Foster City, CA). The newly obtained sequence revealed the presence of a MET start codon (amino acid number 1 of SEQ. NO. 2), a secretion signal (amino acid numbers 4-21 of SEQ. NO. 2), and the remaining portion of the ligand binding domain including a characteristic cytokine receptor family cysteine pattern (amino acids 25, 35, 65, and 81 of SEQ. NO. 2) located within this region.

Example 4: 3'RACE to obtain complete 3' region of HUMAN OCR10:

A 3' RACE reaction was performed using human spleen and human lung Marathon-Ready™ cDNA from CLONTECH as follows:

The first PCR reaction was carried out with oligonucleotide HUMAN OCR10.5 (NTs 372-395 of SEQ. NO. 1) and the RACE kit oligonucleotide AP1. This reaction produced no visible PCR product.

The second PCR reaction was carried out with oligonucleotide HUMAN OCR10.6 (NTs 414-437 of SEQ. NO. 1) and RACE kit oligonucleotide AP2. This reaction produced multiple bands plus smears. Five microliters of each reaction was loaded on a 1% agarose gel, the gel was denatured and neutralized by standard techniques (See Current Protocols in Molecular Biology, Eds. Ausubel, et al., Greene Publ. Assoc., Wiley-Interscience, NY), dried on a Savant Slab Gel Dryer and hybridized overnight at 45°C with a nested oligonucleotide HUMAN OCR10.7 (NTs 441-465 of SEQ. NO. 1). Both of the 3'-specific RACE reaction smears hybridized to a band of approximately 2500bp. A preparative 1% agarose gel was run and 7 individual slices were cut from varying regions of the smears, including the region corresponding to the 2500bp band that hybridized specifically. The individual slices were purified using QIAEX II Gel Extraction Kit (catalog # 20021, QIAGEN, Valencia, CA) and each of these individual slices plus the original second PCR reaction (not gel-purified) were amplified for a third time with another nested oligonucleotide, HUMAN OCR10.7 (NTs 441-465 of SEQ. NO. 1), and RACE kit oligonucleotide AP2. Again, multiple bands were obtained. Five microliters of each reaction was loaded on a 1% agarose gel, the gel was denatured, neutralized and dried and hybridized overnight at 45°C with nested oligonucleotide HUMAN OCR10.9 (NTs 469-490 of SEQ. NO. 1). This hybridization revealed a specific band of approximately 750bp. A preparative 1% agarose gel was run and this 750bp band was isolated and purified using QIAEX II Gel Extraction Kit. The purified slices were sequenced by standard techniques and the 3' end sequence, corresponding to NTs 686-870 of SEQ. NO. 1, contained a stop codon.

HUMAN OCR10 appears to be a typical member of the cytokine receptor family. It has sequences resembling a secretion signal (amino acids 4-21 of SEQ. NO. 2); a typical cytokine receptor family ligand-binding domain comprised of approximately 200 amino acids that contains in its extracellular domain 4 conserved cysteines (amino acids 25, 35, 65, and 81 of SEQ. NO. 2), a proline hinge motif (PP) at amino acids 122-123 of SEQ. NO. 2, and a characteristic cytokine receptor family WSXWS amino acid pattern (amino acids 214-218 of SEQ. NO. 2). In addition, there is a putative hydrophobic transmembrane domain comprising amino acids 238-255 of SEQ. NO. 2; and a potential Jak-binding region (See Cohen, et al., 1995, Cell 80:237-248) at amino acids 263-278 of SEQ. NO. 2. HUMAN OCR10's most closely related cytokine receptor family members includes, but is not limited to, IL-9 receptor (Genebank Identification No. 632993), the cytokine receptor common β chain (Genebank Identification No. 416868), the EPO receptor (Genebank Identification No. 119524), and leptin receptor (Genebank Identification No. 2760950). All sequences identified above by Genebank Identification Nos. can be obtained from The National Center for Biotechnology Information (NCBI) database by accessing their website address www.ncbi.nlm.nih.gov/entrez/protein.html.

Example 5: Northern analysis to determine expression pattern of HUMAN OCR10.

Four human northern blots (Clontech, Catalog #7760-1; #7759-1; #7767-1; and #7766-1) were hybridized (65ºC overnight in hybridization buffer containing 0.5M Na2HPO4, 20% SDS, 10% BSA, 0.5M EDTA. Blots washed at 65ºC with wash solution containing 2XSSC,

0.1% SDS) with the oligonucleotide designated HUMAN OCR10, the sequence of which corresponds to nucleotides 372-658 of SEQ. ID. NO. 1. The results of this Northern analysis were as follows: Two HUMAN OCR10-specific transcripts corresponding to approximately 5kb and 3kb exhibited high expression in spleen, thymus, peripheral blood leukocytes, and lymph node. One highly expressed OCR10-specific transcript of approximately 1 kb was detected in testis. Lower expression levels of 5kb and 3kb OCR10-specific transcripts were seen in placenta, lung, colon mucosal lining, while the prostate, brain and heart exhibited low levels of expression of an approximately 2kb OCR10-specific transcript.

Example 6: Construction of a HUMAN OCR10-Fc DNA construct.

a) Construction of pZB.HUMAN OCR10 DNA construct: In order to obtain an intact, full length copy of the HUMAN OCR10 cDNA, a standard PCR amplification reaction was performed using human spleen and human lung Marathon Ready cDNA (Clontech, Catalog #7412-1 and #7408-1) as a template. The following flanking oligonucleotides were designed as amplification primers:

5'HUMAN OCR10: 5'-CCAGAAACCCATCAGACTGCCC-3'

3'HUMAN OCR10rc: 5'-CTCCTGACGTCAGGTGATCCAC-3'

A second nested PCR amplification reaction was performed using the PCR product of the first PCR reaction as a template. The following

nested oligonucleotides were designed based on the sequence obtained in Examples 4 and 5 *supra* (SEQ. ID. NO. 1):

5'HUMAN OCR10.nested(EcoRI):
5'-GTACTAGATGAATTCGCAACCACCATGCCGCGTGGCTGGGC-3'

3'HUMAN OCR10.nested(NotI):
5'-GATCAGCATGCGGCCGCATCAGTCAATGTCACTTGAAGTTCCGCTGCAG-3'

The resulting 900bp DNA fragment was gel-purified using QiaexII Gel Extraction Kit (Qiagen Catalog# 20021), then blunt-ended using standard molecular biology techniques. This blunt-ended PCR product was subsequently subcloned into the Zeroblunt vector using the Zeroblunt PCR Cloning Kit (Invitrogen, Catalog# K2700-20). The final DNA construct was designated pZB.HUMAN OCR10.

b) Construction of pMT21.HUMAN OCR10 DNA construct: The pZB.HUMAN OCR10 DNA construct was digested with EcoRI and NotI to release the 900 bp fragment described *supra*. The fragment was gel-purified using the QiaexII Gel Extraction Kit. The fragment was subsequently ligated into the pMT21 vector (also digested with EcoRI and NotI) using standard ligation protocol.

c) Subcloning of OCR10 into pJFE-Fc DNA construct: A standard PCR amplification reaction using the pZB.HUMAN OCR10 DNA construct described *supra* as a template was performed to amplify the extracellular domain of HUMAN OCR10. This extracellular domain

corresponds to nucleotides 1 to 708 of SEQ. ID. NO. 1. The following oligonucleotides were designed for use in this PCR reaction:

5'HUMAN OCR10.nested(EcoRI):

5'-GTACTAGATGAATTCGCAACCACCATGCCGCGTGGCTGGGC

3'HUMAN OCR10rc(SrfI):

5'-ATGCGGCCGCATCAGTCAGCCCGGGCCAGGGTTCCAGCCTTCC-3'

The resulting PCR product was digested with the restriction endonucleases EcoRI and SrfI and then gel purified using the QiaexII kit. The purified DNA fragment was then blunt ended using standard molecular biology techniques. The blunt-ended PCR product was subsequently subcloned into the pJFE.Fc vector which had been previously prepared for ligation by digestion with the restriction endonucleases XbaI and SrfI and then blunt-ended. The final DNA construct was designated pJFE.HUMAN OCR10-Fc. The nucleic acid and deduced amino acid sequences of the HUMAN OCR10-Fc insert are set forth below in SEQ. ID. NO. 3 and 4.

```
                    10          20          30          40          50
                     *   *   *   *   *   *   *   *   *   *   *   *   *
SEQ. ID. NO. 3:ATG CCG CGT GGC TGG GCC GCC CCC TTG CTC CTG CTG CTG CTC CAG GGA GGC TGG GGC
SEQ. ID. NO. 4: M   P   R   G   W   A   A   P   L   L   L   L   L   L   Q   G   G   W   G>

               60          70          80          90          100         110
                *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
TGC CCC GAC CTC GTC TGC TAC ACC GAT TAC CTC CAG ACG GTC ATC TGC ATC CTG GAA
 C   P   D   L   V   C   Y   T   D   Y   L   Q   T   V   I   C   I   L   E>

           120         130         140         150         160         170
            *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
ATG TGG AAC CTC CAC CCC AGC ACG CTC ACC CTT ACC TGG CAA GAC CAG TAT GAA GAG
 M   W   N   L   H   P   S   T   L   T   L   T   W   Q   D   Q   Y   E   E>

                   180         190         200         210         220
                    *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
CTG AAG GAC GAG GCC ACC TCC TGC AGC CTC CAC AGG TCG GCC CAC AAT GCC ACG CAT
 L   K   D   E   A   T   S   C   S   L   H   R   S   A   H   N   A   T   H>

         230         240         250         260         270         280
          *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
GCC ACC TAC ACC TGC CAC ATG GAT GTA TTC CAC TTC ATG GCC GAC GAC ATT TTC AGT
 A   T   Y   T   C   H   M   D   V   F   H   F   M   A   D   D   I   F   S>

             290         300         310         320         330         340
              *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
GTC AAC ATC ACA GAC CAG TCT GGC AAC TAC TCC CAG GAG TGT GGC AGC TTT CTC CTG
 V   N   I   T   D   Q   S   G   N   Y   S   Q   E   C   G   S   F   L   L>

                   350         360         370         380         390
                    *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
GCT GAG AGC ATC AAG CCG GCT CCC CCT TTC AAC GTG ACT GTG ACC TTC TCA GGA CAG
 A   E   S   I   K   P   A   P   P   F   N   V   T   V   T   F   S   G   Q>

         400         410         420         430         440         450
          *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
TAT AAT ATC TCC TGG CGC TCA GAT TAC GAA GAC CCT GCC TTC TAC ATG CTG AAG GGC
 Y   N   I   S   W   R   S   D   Y   E   D   P   A   F   Y   M   L   K   G>

             460         470         480         490         500         510
              *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
AAG CTT CAG TAT GAG CTG CAG TAC AGG AAC CGG GGA GAC CCC TGG GCT GTG AGT CCG
 K   L   Q   Y   E   L   Q   Y   R   N   R   G   D   P   W   A   V   S   P>

                   520         530         540         550         560         570
                    *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
AGG AGA AAG CTG ATC TCA GTG GAC TCA AGA AGT GTC TCC CTC CTC CCC CTG GAG TTC
 R   R   K   L   I   S   V   D   S   R   S   V   S   L   L   P   L   E   F>

                   580         590         600         610         620
                    *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
CGC AAA GAC TCG AGC TAT GAG CTG CAG GTG CGG GCA GGG CCC ATG CCT GGC TCC TCC
 R   K   D   S   S   Y   E   L   Q   V   R   A   G   P   M   P   G   S   S>
```

```
                630         640         650         660         670         680
                 *   *   *   *   *   *   *   *   *   *   *   *
SEQ. ID. NO. 3:TAC CAG GGG ACC TGG AGT GAA TGG AGT GAC CCG GTC ATC TTT CAG ACC CAG TCA GAG
SEQ. ID. NO. 4: Y   Q   G   T   W   S   E   W   S   D   P   V   I   F   Q   T   Q   S   E>

            690         700         710         720         730         740
         *   *   *   *   *   *   *   *   *   *   *   *   *   *
GAG TTA AAG GAA GGC TGG AAC CCT GGC CCG GGC GAG CCC AAA TCT TGT GAC AAA ACT
                                    G   P   G   E   P   K   S   C   D   K   T>
 E   L   K   E   G   W   N   P>

                750         760         770         780         790
             *   *   *   *   *   *   *   *   *   *   *   *   *
CAC ACA TGC CCA CCG TGC CCA GCA CCT GAA CTC CTG GGG GGA CCG TCA GTC TTC CTC
 H   T   C   P   P   C   P   A   P   E   L   L   G   G   P   S   V   F   L>

800         810         820         830         840         850
 *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
TTC CCC CCA AAA CCC AAG GAC ACC CTC ATG ATC TCC CGG ACC CCT GAG GTC ACA TGC
 F   P   P   K   P   K   D   T   L   M   I   S   R   T   P   E   V   T   C>

            860         870         880         890         900         910
             *   *   *   *   *   *   *   *   *   *   *   *   *
GTG GTG GTG GAC GTG AGC CAC GAA GAC CCT GAG GTC AAG TTC AAC TGG TAC GTG GAC
 V   V   V   D   V   S   H   E   D   P   E   V   K   F   N   W   Y   V   D>

                920         930         940         950         960
             *   *   *   *   *   *   *   *   *   *   *   *   *
GGC GTG GAG GTG CAT AAT GCC AAG ACA AAG CCG CGG GAG GAG CAG TAC AAC AGC ACG
 G   V   E   V   H   N   A   K   T   K   P   R   E   E   Q   Y   N   S   T>

970         980         990         1000        1010        1020
 *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
TAC CGT GTG GTC AGC GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG AAT GGC AAG GAG
 Y   R   V   V   S   V   L   T   V   L   H   Q   D   W   L   N   G   K   E>

            1030        1040        1050        1060        1070        1080
             *   *   *   *   *   *   *   *   *   *   *   *   *
TAC AAG TGC AAG GTC TCC AAC AAA GCC CTC CCA GCC CCC ATC GAG AAA ACC ATC TCC
 Y   K   C   K   V   S   N   K   A   L   P   A   P   I   E   K   T   I   S>

                1090        1100        1110        1120        1130        1140
             *   *   *   *   *   *   *   *   *   *   *   *   *
AAA GCC AAA GGG CAG CCC CGA GAA CCA CAG GTG TAC ACC CTG CCC CCA TCC CGG GAT
 K   A   K   G   Q   P   R   E   P   Q   V   Y   T   L   P   P   S   R   D>

                1150        1160        1170        1180        1190
             *   *   *   *   *   *   *   *   *   *   *   *   *
GAG CTG ACC AAG AAC CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC TAT CCC AGC
 E   L   T   K   N   Q   V   S   L   T   C   L   V   K   G   F   Y   P   S>

1200        1210        1220        1230        1240        1250
 *   *   *   *   *   *   *   *   *   *   *   *   *
GAC ATC GCC GTG GAG TGG GAG AGC AAT GGG CAG CCG GAG AAC AAC TAC AAG ACC ACG
 D   I   A   V   E   W   E   S   N   G   Q   P   E   N   N   Y   K   T   T>
```

```
                1260        1270        1280        1290        1300        1310
                 *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
SEQ. ID. NO. 3: CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC TTC CTC TAC AGC AAG CTC ACC GTG GAC
SEQ. ID. NO. 4:  P   P   V   L   D   S   D   G   S   F   F   L   Y   S   K   L   T   V   D>

                    1320        1330        1340        1350        1360
                     *   *   *   *   *   *   *   *   *   *   *   *   *   *
                AAG AGC AGG TGG CAG CAG GGG AAC GTC TTC TCA TGC TCC GTG ATG CAT GAG GCT CTG
                 K   S   R   W   Q   Q   G   N   V   F   S   C   S   V   M   H   E   A   L>

            1370        1380        1390        1400        1410
             *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
            CAC AAC CAC TAC ACG CAG AAG AGC CTC TCC CTG TCT CCG GGT AAA TGA
             H   N   H   Y   T   Q   K   S   L   S   L   S   P   G   K   *>
```

Example 7: Expression of HUMAN OCR10-Fc protein in CHO-K1 (E1A) cells.

a) Construction of pTE003 DNA construct: HUMAN OCR10-Fc was released from pJFE14.HUMAN OCR10.Fc described *supra* by standard digestion of the DNA construct with the restriction endonucleases EcoRI and NotI. The resulting 1438 base pair HUMAN OCR10-Fc band was isolated from a 1% agarose gel using a QIAgen QIA-Quik gel extraction kit, following the manufacturer's protocol. The expression vector pRG763 was also digested with EcoRI and NotI and the linearized vector was isolated from a 1% agarose gel in the same manner.

An approximately 2:1 (insert:vector) ratio of gel purified DNA fragments was mixed and a standard ligation reaction was set up using T4 DNA ligase. The ligation reaction was incubated at 4° overnight. One µl of ligation reaction was combined with 25µl of Electro-competent DH10B E. coli cells (Gibco/BRL). The DNA ligation reaction was electroporated into the cells in a Bio-Rad electroporation device, using standard E. coli electroporation protocols. Following electroporation, 0.9ml of SOC media (Gibco) was added to the cells, which were then incubated at 37° for 1 hour prior to plating of 200 µl on LB/ampicillin plates. The following day, 10 colonies were picked from the LB/amp plates and grown overnight in 1 ml LB media + ampicillin. DNA was prepared from the overnight cultures using a Promega Wizard mini-prep kit, following the manufacturer's protocol. Isolated DNA was screened for the presence of the desired insert by

digestion with EcoRI and NotI. DNA minipreps which contained the proper size EcoRI and NotI fragment were subsequently digested with EagI to verify the presence of the insert. One candidate miniprep plasmid which exhibited the proper size bands in EcoRI + NotI and EagI digestions was sequenced at the insertion junctions. Upon verification of the sequence, this plasmid was named pTE003. A large scale preparation of pTE003 plasmid in DH10B cells was grown overnight in LB + ampicillin (1L) and the plasmid DNA was extracted using a Promega Wizard Maxiprep kit, following the manufacturer's protocol. The concentration of the purified plasmid DNA was determined in a UV spectrophotometer and fluorometer. The plasmid DNA was also verified by digestion of aliquots with NotI, AccI and HincII restriction endonucleases. All restriction endonucleases digest fragments corresponded to the predicted sizes in a 1% agarose gel.

b) Transfection of CHO-K1/E1A cells with pTE003 plasmid: Forty 15 cm petri plates were seeded with CHO-K1/E1A cells at a density of 4 x 10^6 cells/plate. Plating media was Gibco Ham's F-12 with 10% Hyclone Fetal Bovine Serum (FBS) + penicillin/streptomycin and supplemented with glutamine. The following day each plate was transfected with 6 µg of pTE003 using Gibco Optimem and Gibco Lipofectamine in 12 ml volume, following the manufacturer's protocol. Four hours after adding the transfection mix to the cells 12 ml/plate of Optimem w/ 10% FBS was added. Plates were incubated at 37° in a 5% CO_2 incubator overnight. The following day the media was removed from each plate and 25 ml expression media (Gibco CHO-S-SFM II w/ glutamine + 1mM

sodium butyrate) was added. The plates were incubated at 37° for 3 days.

After 3 days of incubation the media was aspirated from each plate and centrifuged at 400 rpm in a swinging bucket rotor to pellet cells. The supernatant was decanted into sterile 1L bottles and purified as described *infra*.

Example 8: Purification of HUMAN OCR10-Fc protein from CHO cell media.

Human OCR10-Fc was expressed as a soluble secreted protein from stable CHO-K1/E1A cells using roller bottle production. Quantitation of expression of the secreted protein was determined using a standard sandwich ELISA. A starting quantity of human OCR10-Fc of 221 mg in 2.4 L of conditioned media (92 mg/L) was determined. To prevent proteolytic breakdown of the protein, protease inhibitor tablets (Roche Diagnostics Corp.) were dissolved into the media (1 tablet/L). The conditioned media was subsequently sterile filtered (0.22 μm pore size, cellulose acetate, Corning) prior to loading onto a pre-equilibrated, packed Protein A column (Amersham Pharmacia Biotech) in Dulbecco's PBS buffer, pH 7.4 at 4 °C (Life Technologies). The bed volume was 25 mL (2.6 cm x 5.0 cm), and the flow rate was ~1-2 mL/min. The column was extensively washed with PBS buffer to remove non-specifically bound proteins from the column. Subsequently, the column was washed with 20 mM sodium citrate, 150 mM NaCl, pH 5.0 to remove most of the bovine IgG from the column. Human OCR10-Fc was eluted using 20 mM sodium citrate, 150 mM NaCl, pH 3.5. The protein was immediately

dialyzed against PBS buffer, pH 7.4 at 4 °C. Following dialysis, the protein yield was determined to be 86 mg (39% recovery). The protein was concentrated to a concentration of 5 mg/ml using a Millipore centrifugal concentrator with a molecular weight cutoff of 30,000 dalton (Millipore Corporation) and further purified by size exclusion chromatography using a Sephacryl S200 26/60 column (Amersham Pharmacia Biotech) (320 mL bed volume; pre-equilibrated in PBS, 5% v/v glycerol, pH 7.4 at ambient temperature). The flow rate was 1 mL/min. Eluted protein fractions were assessed from standard Coomassie-stained non-reduced and reduced SDS-PAGE (Novex NuPage 4-12% Bis-Tris gels). Fractions were conservatively pooled to significantly reduce the amount of aggregated protein. The overall yield was 15.6% (7.1 mg) with a purity of 95% judged by standard SDS-PAGE. Purified HUMAN OCR10-Fc was analyzed by non-reduced and reduced SDS-PAGE (4-12% Bis-Tris), analytical size exclusion chromatography (Tosohaas TSKG4000SWXL, N-terminal sequencing, and immunoblotting with goat anti-hIgG-HRP conjugate (Promega W403B).

Example 9: Identification of the putative long form of HUMAN OCR10 designated HUMAN OCR10-A.

The first evidence for the long form of HUMAN OCR10 was obtained by searching the Human Virtual Transcribed Sequence database (Kazusa DNA Research Institute, http://zearth.kazusa.or.jp/vts/intro.html) with the HUMAN OCR10, using the blastp algorithm from NIH. This database contains protein sequences that are predicted to be encoded by the human genomic sequences collected from public sources.

Example 10: RT-PCR to amplify the C-terminal of HUMAN OCR10-A.

Two oligonucleotides designated HUMAN OCR10-oligo-1, corresponding to nucleotides 575-597 of SEQ. ID. NO. 1, and HUMAN OCR10-oligo-3 corresponding to nucleotides 1617-1600 of SEQ. ID. NO. 5 and containing a Spe I cloning site (ATACTAG TTAGCTGGCCTGGGGTCC), were synthesized (Genelink, Thornwood, NY) and used as amplification primers in a standard RT-PCR reaction. In the RT reaction, 5 μg of total RNA derived from the Wilz-NS cell line and 0.1 μmoles of HUMAN OCR10-oligo-3 were used to synthesize cDNA. A PCR reaction was subsequently carried out using oligonucleotides HUMAN OCR10-oligo-1 and HUMAN OCR10-oligo-3 and one tenth of the cDNA synthesized in the RT reaction described above as a template. The PCR reaction product was run on a preparative 1% agarose gel, and a slice containing a 1kb DNA fragment was cut out and purified using QIAquick Gel Extraction Kit, (Catalog #28704, QIAGEN, Valencia, CA). The purified fragment was subcloned using standard molecular biology techniques into the commercially available pCR2.1-TOPO vector (Catalog #4500-01, Invitrogen, Carlsbad, CA). Standard plasmid minipreps were performed on 6 bacterial transformants using the QIAprep Spin Miniprep Kit (Catalog #27104, QIAGEN, Valencia, CA). The DNA inserts in the six transformants were sequenced by standard techniques using an ABI 373A DNA sequencer and Taq Dideoxy Terminator Cycle Sequencing Kit (Applied Biosystems, Inc., Foster City, CA). The nucleotide and deduced amino acid sequences of one of the clones, designated #116, revealed a sequence corresponding to nucleotides 575-1617 of SEQ. ID. NO. 5 and amino acids residues 192-538 of SEQ. NO. 6, respectively, as set forth below.

```
                    10          20          30          40          50
                     *   *   *   *   *   *   *   *   *   *   *   *   *
SEQ. ID. NO. 5: ATG CCG CGT GGC TGG GCC GCC CCC TTG CTC CTG CTG CTG CTC CAG GGA GGC TGG GGC
SEQ. ID. NO. 6:  M   P   R   G   W   A   A   P   L   L   L   L   L   L   Q   G   G   W   G>

                60          70          80          90          100         110
                 *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
                TGC CCC GAC CTC GTC TGC TAC ACC GAT TAC CTC CAG ACG GTC ATC TGC ATC CTG GAA
                 C   P   D   L   V   C   Y   T   D   Y   L   Q   T   V   I   C   I   L   E>

            120         130         140         150         160         170
             *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
            ATG TGG AAC CTC CAC CCC AGC ACG CTC ACC CTT ACC TGG CAA GAC CAG TAT GAA GAG
             M   W   N   L   H   P   S   T   L   T   L   T   W   Q   D   Q   Y   E   E>

                180         190         200         210         220
                 *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
                CTG AAG GAC GAG GCC ACC TCC TGC AGC CTC CAC AGG TCG GCC CAC AAT GCC ACG CAT
                 L   K   D   E   A   T   S   C   S   L   H   R   S   A   H   N   A   T   H>

            230         240         250         260         270         280
             *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
            GCC ACC TAC ACC TGC CAC ATG GAT GTA TTC CAC TTC ATG GCC GAC GAC ATT TTC AGT
             A   T   Y   T   C   H   M   D   V   F   H   F   M   A   D   D   I   F   S>

                290         300         310         320         330         340
                 *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
                GTC AAC ATC ACA GAC CAG TCT GGC AAC TAC TCC CAG GAG TGT GGC AGC TTT CTC CTG
                 V   N   I   T   D   Q   S   G   N   Y   S   Q   E   C   G   S   F   L   L>

                350         360         370         380         390
                 *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
                GCT GAG AGC ATC AAG CCG GCT CCC CCT TTC AAC GTG ACT GTG ACC TTC TCA GGA CAG
                 A   E   S   I   K   P   A   P   P   F   N   V   T   V   T   F   S   G   Q>

            400         410         420         430         440         450
             *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
            TAT AAT ATC TCC TGG CGC TCA GAT TAC GAA GAC CCT GCC TTC TAC ATG CTG AAG GGC
             Y   N   I   S   W   R   S   D   Y   E   D   P   A   F   Y   M   L   K   G>

                460         470         480         490         500         510
                 *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
                AAG CTT CAG TAT GAG CTG CAG TAC AGG AAC CGG GGA GAC CCC TGG GCT GTG AGT CCG
                 K   L   Q   Y   E   L   Q   Y   R   N   R   G   D   P   W   A   V   S   P>

                520         530         540         550         560         570
                 *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
                AGG AGA AAG CTG ATC TCA GTG GAC TCA AGA AGT GTC TCC CTC CTC CCC CTG GAG TTC
                 R   R   K   L   I   S   V   D   S   R   S   V   S   L   L   P   L   E   F>

                580         590         600         610         620
                 *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
                CGC AAA GAC TCG AGC TAT GAG CTG CAG GTG CGG GCA GGG CCC ATG CCT GGC TCC TCC
                 R   K   D>
                            S   S   Y   E   L   Q   V   R   A   G   P   M   P   G   S   S>
```

```
                630         640         650         660         670         680
                 *   *   *   *   *   *   *   *   *   *   *   *   *
SEQ. ID. NO. 5: TAC CAG GGG ACC TGG AGT GAA TGG AGT GAC CCG GTC ATC TTT CAG ACC CAG TCA GAG
SEQ. ID. NO. 6:  Y   Q   G   T   W   S   E   W   S   D   P   V   I   F   Q   T   Q   S   E>

                690         700         710         720         730         740
             *   *   *   *   *   *   *   *   *   *   *   *   *   *
             GAG TTA AAG GAA GGC TGG AAC CCT CAC CTG CTG CTT CTC CTC CTG CTT GTC ATA GTC
              E   L   K   E   G   W   N   P   H   L   L   L   L   L   L   V   I   V>

                    750         760         770         780         790
                 *   *   *   *   *   *   *   *   *   *   *   *   *
                 TTC ATT CCT GCC TTC TGG AGC CTG AAG ACC CAT CCA TTG TGG AGG CTA TGG AAG AAG
                  F   I   P   A   F   W   S   L   K   T   H   P   L   W   R   L   W   K   K>

            800         810         820         830         840         850
             *   *   *   *   *   *   *   *   *   *   *   *   *   *
             ATA TGG GCC GTC CCC AGC CCT GAG CGG TTC TTC ATG CCC CTG TAC AAG GGC TGC AGC
              I   W   A   V   P   S   P   E   R   F   F   M   P   L   Y   K   G   C   S>

                860         870         880         890         900         910
                 *   *   *   *   *   *   *   *   *   *   *   *   *
                 GGA GAC TTC AAG AAA TGG GTG GGT GCA CCC TTC ACT GGC TCC AGC CTG GAG CTG GGA
                  G   D   F   K   K   W   V   G   A   P   F   T   G   S   S   L   E   L   G>

                    920         930         940         950         960
                 *   *   *   *   *   *   *   *   *   *   *   *   *
                 CCC TGG AGC CCA GAG GTG CCC TCC ACC CTG GAG GTG TAC AGC TGC CAC CCA CCA CGG
                  P   W   S   P   E   V   P   S   T   L   E   V   Y   S   C   H   P   P   R>

           970         980         990         1000        1010        1020
            *   *   *   *   *   *   *   *   *   *   *   *   *   *
            AGC CCG GCC AAG AGG CTG CAG CTC ACG GAG CTA CAA GAA CCA GCA GAG CTG GTG GAG
             S   P   A   K   R   L   Q   L   T   E   L   Q   E   P   A   E   L   V   E>

                1030        1040        1050        1060        1070        1080
                 *   *   *   *   *   *   *   *   *   *   *   *   *
                 TCT GAC GGT GTG CCC AAG CCC AGC TTC TGG CCG ACA GCC CAG AAC TCG GGG GGC TCA
                  S   D   G   V   P   K   P   S   F   W   P   T   A   Q   N   S   G   G   S>

                    1090        1100        1110        1120        1130        1140
                 *   *   *   *   *   *   *   *   *   *   *   *   *
                 GCT TAC AGT GAG GAG AGG GAT CGG CCA TAC GGC CTG GTG TCC ATT GAC ACA GTG ACT
                  A   Y   S   E   E   R   D   R   P   Y   G   L   V   S   I   D   T   V   T>

                        1150        1160        1170        1180        1190
                     *   *   *   *   *   *   *   *   *   *   *   *   *
                     GTG CTA GAT GCA GAG GGG CCA TGC ACC TGG CCC TGC AGC TGT GAG GAT GAC GGC TAC
                      V   L   D   A   E   G   P   C   T   W   P   C   S   C   E   D   D   G   Y>

                1200        1210        1220        1230        1240        1250
                 *   *   *   *   *   *   *   *   *   *   *   *   *
                 CCA GCC CTG GAC CTG GAT GCT GGC CTG GAG CCC AGC CCA GGC CTA GAG GAC CCA CTC
                  P   A   L   D   L   D   A   G   L   E   P   S   P   G   L   E   D   P   L>
```

```
                    1260          1270          1280          1290          1300          1310
                     *     *       *     *       *     *       *     *       *     *       *     *
SEQ. ID. NO. 5:  TTG GAT GCA GGG ACC ACA GTC CTG TCC TGT GGC TGT GTC TCA GCT GGC AGC CCT GGG
SEQ. ID. NO. 6:   L   D   A   G   T   T   V   L   S   C   G   C   V   S   A   G   S   P   G>

                          1320          1330          1340          1350          1360
                           *     *       *     *       *     *       *     *       *     *
                  CTA GGA GGG CCC CTG GGA AGC CTC CTG GAC AGA CTA AAG CCA CCC CTT GCA GAT GGG
                   L   G   G   P   L   G   S   L   L   D   R   L   K   P   P   L   A   D   G>

             1370          1380          1390          1400          1410          1420
              *     *       *     *       *     *       *     *       *     *       *     *
            GAG GAC TGG GCT GGG GGA CTG CCC TGG GGT GGC CGG TCA CCT GGA GGG GTC TCA GAG
             E   D   W   A   G   G   L   P   W   G   G   R   S   P   G   G   V   S   E>

               1430          1440          1450          1460          1470          1480
                *     *       *     *       *     *       *     *       *     *       *     *
            AGT GAG GCG GGC TCA CCC CTG GCC GGC CTG GAT ATG GAC ACG TTT GAC AGT GGC TTT
             S   E   A   G   S   P   L   A   G   L   D   M   D   T   F   D   S   G   F>

                    1490          1500          1510          1520          1530
                     *     *       *     *       *     *       *     *       *     *
                  GTG GGC TCT GAC TGC AGC AGC CCT GTG GAG TGT GAC TTC ACC AGC CCC GGG GAC GAA
                   V   G   S   D   C   S   S   P   V   E   C   D   F   T   S   P   G   D   E>

            1540          1550          1560          1570          1580          1590
             *     *       *     *       *     *       *     *       *     *       *     *
            GGA CCC CCC CGG AGC TAC CTC CGC CAG TGG GTG GTC ATT CCT CCG CCA CTT TCG AGC
             G   P   P   R   S   Y   L   R   Q   W   V   V   I   P   P   P   L   S   S>

               1600          1610
                *     *       *     *
            CCT GGA CCC CAG GCC AGC TAA
             P   G   P   Q   A   S   *>
```

Example 11: Cloning of HUMAN OCR10-A.

Plasmid pMT21-HUMAN OCR10 contains sequence corresponding to nucleotides 1-867 of SEQ. ID. NO. 1. This plasmid DNA was digested with the restriction endonucleases Xho I and Spe I to release a fragment of DNA which contains pMT21 vector (Genetics Institute, Inc., Cambridge MA) plus partial HUMAN OCR10 sequence corresponding to nucleotides 1-579 of SEQ. ID. NO. 1. This DNA fragment was purified using a 0.7 % preparative agarose gel using the QIAquick Gel Extraction Kit. The insert of clone #116 described *supra* was released from the vector pCR2.1-TOPO by digesting it with the restriction endonucleases Xho I and Spe I. This 1057bp DNA fragment containing nucleotides 575-1617 of SEQ. ID. NO. 5 was purified using a 0.7 % preparative agarose gel using the QIAquick Gel Extraction Kit. A standard ligation reaction was carried out to ligate the to gel purified fragments, and subsequent standard bacterial transformation was performed. The resulting plasmid, designated pMT21-HUMAN OCR10-A, was sequenced by standard techniques using an ABI 373A DNA sequencer and Taq Dideoxy Terminator Cycle Sequencing Kit (Applied Biosystems, Inc., Foster City, CA). It contains the nucleotide and deduced amino acid sequences corresponding to nucleotides 1-1617 of SEQ. ID. NO. 5 and amino acids 1-538 of SEQ. ID. NO. 6, respectively.

Example 12: Northern analysis to determine expression pattern of HUMAN OCR10-A.

Three Clonetech Human Northern Blots (catalog#'s: 7760-1; 7759-1; and 7767-1) were hybridized as described *supra* with an oligonucleotide designated HUMAN OCR10vts which corresponds to nucleotides 901-1593 of SEQ. ID. NO. 5. The results of this northern analysis were as follows: Two HUMAN OCR10-specific transcripts corresponding to approximately 5kb and 3kb exhibited high expression in spleen, thymus, peripheral blood leukocytes, and lymph node. One highly expressed OCR10-A-specific transcript of approximately 2.4 kb was detected in testis. Lower expression levels of 5kb and 3kb OCR10-A-specific transcripts were seen in placenta, lung, colon mucosal lining. The prostate has lower levels of expression of a transcript of approximately 3kb. These results are similar to those observed with HUMAN OCR10, with the exception of testis and prostate, each of which exhibit larger transcript sizes in the HUMAN OCR10-A Northern analysis.

HUMAN OCR10 and Human OCR10-A both appear to be a receptors for a known or novel cytokine. It may be used either to identify and clone the novel cytokine, or to control the signaling by the known one. The high expression observed in tissue related to the immune system (i.e. thymus, peripheral blood leukocytes, and lymph node) and the fact that HUMAN OCR10 maps to chromosome 16p12 just 90kb from the chromosomal location of IL4Rα indicate that this receptor has a role in immunity and cytokine function.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the

invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

5

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule encoding HUMAN OCR10.

2. An isolated nucleic acid molecule according to claim 1, having a sequence selected from the group consisting of:

(a) the nucleotide sequence comprising the coding region of the HUMAN OCR10 as set forth in SEQ. NO. 1;

(b) a nucleotide sequence that hybridizes under stringent conditions to the nucleotide sequence of (a) and which encodes a molecule having the activity of the HUMAN OCR10; or

(c) a nucleotide sequence which, but for the degeneracy of the genetic code would hybridize to a nucleotide sequence of (a) or (b), and which encodes a molecule having the activity of the HUMAN OCR10.

3. A vector which comprises a nucleic acid molecule of claim 1.

4. A vector according to claim 3, wherein the nucleic acid molecule is operatively linked to an expression control sequence capable of directing its expression in a host cell.

5. An isolated nucleic acid molecule encoding a HUMAN OCR10.

6. Isolated HUMAN OCR10 polypeptide.

7. Isolated HUMAN OCR10 polypeptide encoded by the nucleic acid molecule of claim 2.

8. A host-vector system for the production of HUMAN OCR10 polypeptide which comprises a vector of claim 4, in a host cell.

9. A host-vector system according to claim 8, wherein the host cell is a bacterial, yeast, insect or mammalian cell.

10. A method of producing HUMAN OCR10 polypeptide which comprise growing cells of a host-vector system of claim 9, under Conditions permitting the production of HUMAN OCR10 polypeptide And recovering the HUMAN OCR10 polypeptide so produced.

11. An antibody which specifically binds HUMAN OCR10 polypeptide of claim 6.

12. An antibody according to claim 11, which is a monoclonal antibody.

13. A composition comprising HUMAN OCR10 polypeptide according to claim 7 and a carrier.

14. A composition comprising an antibody according to claim 11, and a carrier.

15. A composition comprising the extracellular portion of the HUMAN OCR10 polypeptide fused to an immunoglobulin constant region.

16. The composition of claim 15, wherein the constant region is the human immunoglobulin gamma-1 constant region.

17. A composition comprising the extracellular portion of the HUMAN OCR10 polypeptide fused to an immunoglobulin Fc region.

18. The composition of claim 17, wherein the Fc region is the human immunoglobulin gamma-1 Fc region.

19. An isolated nucleic acid molecule encoding HUMAN OCR10-A.

20. An isolated nucleic acid molecule according to claim 19, having a sequence selected from the group consisting of:

(a) the nucleotide sequence comprising the coding region of the HUMAN OCR10-A as set forth in SEQ. NO. 5;

(b) a nucleotide sequence that hybridizes under stringent conditions to the nucleotide sequence of (a) and which encodes a molecule having the activity of the HUMAN OCR10-A; or

(c) a nucleotide sequence which, but for the degeneracy of the genetic code would hybridize to a nucleotide sequence of (a) or (b), and which encodes a molecule having the activity of the HUMAN OCR10-A.

21. A vector which comprises a nucleic acid molecule of claim 19.

22. A vector according to claim 21, wherein the nucleic acid molecule is operatively linked to an expression control sequence capable of directing its expression in a host cell.

23. An isolated nucleic acid molecule encoding a HUMAN OCR10-A.

24. Isolated HUMAN OCR10-A polypeptide.

25. Isolated HUMAN OCR10-A polypeptide encoded by the nucleic acid molecule of claim 20.

26. A host-vector system for the production of HUMAN OCR10-A polypeptide which comprises a vector of claim 22, in a host cell.

27. A host-vector system according to claim 26, wherein the host cell is a bacterial, yeast, insect or mammalian cell.

28. A method of producing HUMAN OCR10-A polypeptide which comprise growing cells of a host-vector system of claim 27, under conditions permitting the production of HUMAN OCR10-A polypeptide and recovering the HUMAN OCR10-A polypeptide so produced.

29. An antibody which specifically binds HUMAN OCR10-A polypeptide of claim 24.

30. An antibody according to claim 29, which is a monoclonal antibody.

31. A composition comprising HUMAN OCR10-A polypeptide according to claim 25 and a carrier.

32. A composition comprising an antibody according to claim 29, and a carrier.

INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/US 99/16060

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C12N15/62 C12N5/10 C12N1/21 C07K14/715
C07K16/28 A61K38/17 A61K39/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 99 47675 A (GENETICS INST) 23 September 1999 (1999-09-23) abstract seq ID 1 (nt 236-1102) claims 1-25	1-32

X	DATABASE EMBL SEQUENCES 'Online! EMBL, Heidelberg, FRG Accession No. AC002303, 26 June 1997 (1997-06-26) ADAMS M.D.: "H. sapiens genomic sequence, Chromosome 16 BAC clone CIT987-SKA-670B5" XP002111162 cited in the application nt 33765-33965 are identical to nt 152-352 of seq. ID 1	1-32

	-/—	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 January 2000	18/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx 31 651 epo nl, Fax: (+31-70) 340-3016	Galli, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/US 99/16060

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 31811 A (DONALDSON DEBRA D ;GENETICS INST (US); COLLINS MARY (US); NEBEN TA) 23 July 1998 (1998-07-23) abstract page 4, line 9 - line 12 ---	1-32
A	O'DOWD B F ET AL: "Cloning and chromosomal mapping of four putative novel human G-protein-coupled receptor genes" GENE: AN INTERNATIONAL JOURNAL ON GENES AND GENOMES,GB,ELSEVIER SCIENCE PUBLISHERS, BARKING, vol. 187, no. 1, 1997, page 75-81 XP004093242 ISSN: 0378-1119 the whole document ---	1-32
A	BAZAN J F: "Structural design and molecular evolution of a cytokine receptor superfamily" JOURNAL OF BIOLOGICAL CHEMISTRY,US,AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 87, September 1990 (1990-09), page 6934-6938-6938 XP002111161 ISSN: 0021-9258 cited in the application the whole document ---	1-32
A	WO 98 11225 A (NICOLA NICOS ANTONY ;FABRI LOUIS (AU); FARLEY ALISON (AU); NASH AN) 19 March 1998 (1998-03-19) abstract examples 2,7 ---	1-32
A	US 5 447 851 A (BEUTLER BRUCE A ET AL) 5 September 1995 (1995-09-05) the whole document -----	15-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/16060

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9947675 A	23-09-1999	NONE	
WO 9831811 A	23-07-1998	AU 5733898 A	07-08-1998
WO 9811225 A	19-03-1998	AU 4308097 A	02-04-1998
		EP 0931149 A	28-07-1999
US 5447851 A	05-09-1995	NONE	